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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,415	01/26/2005	Vivian I Teichberg	29147	5568

7590 01/11/2007

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EXAMINER	
GOUGH, TIFFANY MAUREEN	
ART UNIT	PAPER NUMBER
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,415	TEICHBERG, VIVIAN I	
	Examiner	Art Unit	
	Tiffany M. Gough	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10-15,26 and 120-127* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10-15,26 and 120-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application
6)☐ Other: _____.

DETAILED ACTION

Applicant's response filed 10/12/2006 has been received and entered into the case. New claims 120-127 have been entered into the instant application. Claims 1-4,10-15 26,120-127 are pending and have been considered on the merits. All arguments and amendments have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-15 and 125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant claims an enzyme selected incapable of converting modified glutamate into glutamate. This in itself is confusing for the reason that one would not need an enzyme to convert glutamate to glutamate and further lacks antecedent basis because claims 1 and 122 do not claim a modified glutamate.

Applicants amendments to the claims fails to clarify the above rejection, thus the rejection remains on the above amended claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4,10-15,120-127 rejected under 35 U.S.C. 103(a) as being unpatentable over Matthews et al (Journal of Neurochemistry, vol75, 2000) in view of http://www.bio.mtu/edu/campbell/bl4820/lectures/lec4/gotw41.htm,1996 and http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html.

Applicant claims a method of reducing extracellular brain glutamate levels by administering, to a subject in need of, an effective amount not exceeding 1g/kg body weight, of a naturally occurring or artificially modified glutamate modifying enzyme, specifically a transaminase and a co-factor of the enzyme.

Matthews et al teach the involvement of glutamate in neuronal death or injury associated with elevated extracellular glutamate levels in diseases such as ischemic brain injury, stroke, ALS, Parkinson's and Alzheimer's disease. They teach the enzymatic degradation of glutamate by GPT, which is useful in protecting the neurons from excitotoxic injury (see abstract). Their examples teach decreased levels of glutamate when incubated with GPT and its respective co-substrates and cofactors, pyridoxal phosphate and pyruvate. Results show glutamate degradation, therefore they expect GPT to provide useful protection against glutamate neurotoxicity associated with patients suffering from ischemic brain injury, stroke, ALS, Parkinson's and Alheimer's disease. Therefore, Matthews discloses the ability of GPT, a glutamate modifying enzyme, to decrease extracellular glutamate levels associated with the related disorders and diseases, i.e. a subject in need thereof.

Matthews do not teach administering to a subject in need thereof a glutamate modifying enzyme, however, they do teach diseases associated with elevated extracellular glutamate levels and further teach a decrease in glutamate levels when incubated with a glutamate modifying enzyme GPT and it's respective substrates and co-factors. Thus, it would have been obvious to one of ordinary skill in the art, at the time of the claimed invention to administer a glutamate modifying enzyme to a subject in need thereof, such as one suffering from the diseases taught by Matthews associated with elevated extracellular glutamate levels because Matthews et al teach the GPT to be successful in decreasing elevated glutamate levels.

Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to have administered a glutamate modifying enzyme to a subject in need thereof with a reasonable expectation for successfully decreasing extracellular glutamate levels because Matthews teach GPT to be useful in decreasing glutamate levels and useful in protecting against glutamate neurotoxicity associated with patients suffering from ischemic brain injury, stroke, ALS, Parkinson's and Alheimer's disease.

Matthews does not disclose the GPT to be artificially modified, however, protein engineering, i.e, modification, is well known in the art. For support see Haring et al , Protein Engineering, vol.15, 2002, who teach assembling artificial transaminases.

Further, Matthews does not teach administering GOT.

http://www.bio.mtu/edu/campbell/bl4820/lectures/lec4/gotw41.htm teaches pyridoxal phosphate to be a cofactor for GOT as well as the co-substrate oxaloacetate

along with glutamate. Both enzymes GPT and GOT use glutamate as a substrate and pyridoxal phosphate as their cofactor to reversibly convert glutamate into 2-keto-glutarate (see http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html). Thus, given what is taught by Matthews of GPT's ability to reduce glutamate levels and the similarities of GPT and GOT, i.e both glutamate converting enzymes using pyridoxal phosphate as their cofactor, differing only in their substrates pyruvate and oxaloacetate, it would have been obvious to one of ordinary skill in the art at the time of the invention to administer GOT, along with its respective cofactors and co-substrates, pyridoxal phosphate and oxaloacetate, to reduce extracellular glutamate levels in a subject in need given what is taught by Matthews et al of GPT's ability to reduce glutamate levels along with its respective cofactors and substrates.

Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to have administered a glutamate modifying enzyme such as GOT to a subject in need thereof with a reasonable expectation for successfully decreasing extracellular glutamate levels because Matthews teach GPT to be useful in decreasing glutamate levels and useful in protecting against glutamate neurotoxicity associated with patients suffering from ischemic brain injury, stroke, ALS, Parkinson's and Alheimer's disease, further motivation is provided by the fact that both enzymes, GPT and GOT, use glutamate as a substrate and pyridoxal phosphate as their cofactor to reversibly convert glutamate into 2-keto-glutarate.

Claims 1-4,10-15,26,120-125 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/21565 in view of Matthews et al (Journal of Neurochemistry, vol75, 2000) and http://www.bio.mtu/edu/campbell/bl4820/lectures/lec4/gotw41.htm,1996, http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html,1976.

Applicant claims a method of reducing extracellular brain glutamate levels by administering, to a subject in need of, an effective amount not exceeding 1g/kg body weight, of a glutamate modifying enzyme and/or a co-factor of the enzyme.

WO 99/21565 discloses a method of treating individuals with disorders related to impaired mitochondrial and cerebral function. Such disorders include Huntington's disease which is a neurodegenerative disorder contributed by glutamate-induced neuronal death.

WO '565 discloses treating such disorders by administering a nutritional supplement/pharmaceutical composition in amounts of up to 15 g, containing a Kreb's cycle intermediate, such as oxaloacetic acid (oxaloacetate, a glutamate modifying enzyme co-factor) which is used to treat an individual with disorders related to impaired mitochondrial and cerebral function associated with glutamate excitotoxicity. Such disorders include Huntington's disease which is a neurodegenerative disorder contributed by glutamate-induced neuronal death.

http://www.bio.mtu/edu/campbell/bl4820/lectures/lec4/gotw41.htm teaches pyridoxal phosphate to be a cofactor for GOT as well as the co-substrate oxaloacetate along with glutamate. Both enzymes GPT and GOT use glutamate as a substrate and

pyridoxal phosphate as their cofactor to reversibly convert glutamate into 2-keto-glutarate (see http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html). Thus, given what is taught by Matthews of GPT's ability to reduce glutamate levels and the similarities of GPT and GOT, i.e both glutamate converting enzymes using pyridoxal phosphate as their cofactor, differing only in their substrates pyruvate and oxaloacetate, it would have been obvious to one of ordinary skill in the art at the time of the invention to administer GOT, along with its respective cofactors and co-substrates, pyridoxal phosphate and oxaloacetate, to reduce extracellular glutamate levels in a subject in need given what is taught by Matthews et al of GPT's ability to reduce glutamate levels along with its respective cofactors and substrates.

WO'565 does not teach administering a glutamate modifying enzyme, particularly an artificially modified enzyme, to a subject in need thereof.

However, as stated above Matthews et al teach the glutamate modifying enzyme, GPT to decrease glutamate levels when incubated along with its substrate and co-factors. They further suggest GPT to provide useful protection against glutamate neurotoxicity associated with patients suffering from ischemic brain injury, stroke, ALS, Parkinson's and Alheimer's disease. Further, protein engineering, i.e, modification, is well known in the art. For support see Haring et al, Protein Engineering, vol.15, 2002, who teach assembling artificial transaminases.

Given what is known in the art of the enzymatic reactions of GPT and GOT, it would have been obvious to one of ordinary skill in the art to administer a glutamate modifying enzyme, particularly GOT, it's cofactors and substrates, to a subject in need

to reduce extracellular glutamate levels. Further, WO'565 teaches treating disorders associated with glutamate excitotoxicity by administering oxaloacetate, a glutamate modifying enzyme co-factor, in amounts of 15g, to a subject in need thereof.

Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to have administered a glutamate modifying enzyme such as GOT, it's cofactors and substrates to a subject in need thereof with a reasonable expectation for successfully decreasing extracellular glutamate levels because Matthews teach GPT, it's cofactors and substrates to be useful in decreasing glutamate levels and useful in protecting against glutamate neurotoxicity associated with patients suffering from ischemic brain injury, stroke, ALS, Parkinson's and Alheimer's disease. WO'565 also teach treating those in need by administering the GOT cofactor/substrate oxaloacetate, thus reducing blood glutamate levels is intrinsic to the oxaloacetic acid/oxaloacetate. Thus, by practicing the method of WO '565 one would inherently be practicing the method as claimed. Further motivation is provided by the fact that both enzymes, GPT and GOT, use glutamate as a substrate and pyridoxal phosphate as their cofactor to reversibly convert glutamate into 2-keto-glutarate.

Claims 1-4,10,12-15,26,120,122,124,125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthews et al (Journal of Neurochemistry, vol75, 2000) in view of Geng et al (J. of Neurochemistry, vol. 68, no.6, 1997) and http://www.bio.mtu/edu/campbell/bl4820/lectures/lec4/gotw41.htm,1996, http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html,1976.

Applicant claims a method of reducing extracellular brain glutamate levels by administering, to a subject in need of, an effective amount not exceeding 1g/kg body weight, of a naturally occurring or artificially modified glutamate modifying enzyme, specifically a transaminase and a co-factor of the enzyme.

As stated above Matthews et al teach the glutamate modifying enzyme, GPT to decrease glutamate levels when incubated along with its substrate and co-factors. They further suggest GPT to provide useful protection against glutamate neurotoxicity associated with patients suffering from ischemic brain injury, stroke, ALS, Parkinson's and Alheimer's disease. Further, protein engineering, i.e, modification, is well known in the art. For support see Haring et al, Protein Engineering, vol.15, 2002, who teach assembling artificial transaminases.

Matthews does not teach administering GOT.

http://www.bio.mtu/edu/campbell/bl4820/lectures/lec4/gotw41.htm teaches pyridoxal phosphate to be a cofactor for GOT as well as the co-substrate oxaloacetate along with glutamate. Both enzymes GPT and GOT use glutamate as a substrate and pyridoxal phosphate as their cofactor to reversibly convert glutamate into 2-keto-glutarate (see http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html). Thus, given what is taught by Matthews of GPT's ability to reduce glutamate levels and the similarities of GPT and GOT, i.e both glutamate converting enzymes using pyridoxal phosphate as their cofactor, differing only in their substrates pyruvate and oxaloacetate, it would have been obvious to one of ordinary skill in the art at the time of the invention to administer GOT, along with its respective cofactors and co-substrates, pyridoxal

phosphate and oxaloacetate, to reduce extracellular glutamate levels in a subject in need given what is taught by Matthews et al of GPT's ability to reduce glutamate levels along with its respective cofactors and substrates.

Geng teaches the administration of pyridoxal phosphate to epileptic patients. The increased glutamate levels, associated with elevated extracellular load of glutamate (see abstract), were normalized, thus reduced, by the administration of vitamin B6, i.e. pyridoxal phosphate (see p.2503, second paragraph) in amounts not exceeding 1g/kg (seep.2502).

Given what is known in the art of the enzymatic reactions of GPT and GOT, it would have been obvious to one of ordinary skill in the art to administer a glutamate modifying enzyme, particularly GOT, it's cofactors and substrates, to a subject in need to reduce extracellular glutamate levels. Further because Geng teaches the administration of pyridoxal phosphate to epileptic patients which normalized elevated extracellular load of glutamate (see abstract), it would be obvious to administer such co-factor along with it's respective glutamate converting enzyme, such as GOT.

Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to have administered a glutamate modifying enzyme such as GOT, it's cofactors and substrates to a subject in need thereof with a reasonable expectation for successfully decreasing extracellular glutamate levels because Matthews teach GPT to be useful in decreasing glutamate levels and useful in protecting against glutamate neurotoxicity associated with patients suffering from ischemic brain injury, stroke, ALS, Parkinson's and Alheimer's disease. Geng further

teaches the administration of pyridoxal phosphate to epileptic patients, which normalized elevated extracellular load of glutamate (see abstract). Thus one would have been motivated by the art to administer a glutamate modifying enzyme in combination with its respectibe cofactors and substrates.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tiffany M. Gough whose telephone number is 571-272-0697. The examiner can normally be reached on M-F 8-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Tiffany Gough

RUTH DAVIS
PRIMARY EXAMINER